Differential Impacts of Blood Pressure and Lipid Lowering on Regression of Ventricular and Arterial Mass
The Stop Atherosclerosis in Native Diabetics Trial

Mary J. Roman, Barbara V. Howard, Wm. James Howard, Mihriye Mete, Jerome L. Fleg, Elisa T. Lee, Richard B. Devereux

Abstract—The relative impacts of lowering blood pressure versus lowering low-density lipoprotein (LDL) cholesterol on regression of ventricular and arterial mass have not been systematically examined. Changes in left ventricular mass and arterial mass (common carotid artery cross-sectional area) after 36 months of simultaneous lowering of systolic blood pressure and LDL cholesterol were examined in the Stop Atherosclerosis in Native Diabetics Trial of standard versus aggressive LDL cholesterol and blood pressure targets in American Indians with type 2 diabetes mellitus. The 2 treatment groups were combined to examine changes in left ventricular and arterial mass over a spectrum of achieved blood pressure and lipid levels. Among the combined group of 413 Stop Atherosclerosis in Native Diabetics Trials participants, systolic blood pressure, LDL cholesterol, and left ventricular mass were all significantly reduced, whereas arterial mass significantly increased, after 36 months of therapy (P<0.001 for all). In linear regression models, a decrease in arterial mass was significantly related to achieved systolic blood pressure and, to a lesser extent, achieved LDL cholesterol, after adjustment for important covariates. Left ventricular mass progressively decreased with lower achieved levels of systolic blood pressure, independent of baseline levels of left ventricular mass. In conclusion, achieved levels of systolic blood pressure are important determinants of the extent of regression of arterial and ventricular mass during prolonged therapy in diabetic individuals. Achieved levels of LDL cholesterol influence regression of arterial but not ventricular mass. Our findings suggest that there is no threshold of systolic blood pressure below which regression of cardiovascular target organ damage cannot be achieved. (Hypertension. 2011;58:00-00.)

Key Words: hypertrophy/remodeling ■ atherosclerosis ■ target organ damage

Both dyslipidemia and hypertension contribute to abnormal increases in carotid artery intimal-medial thickness (IMT) and mass (cross-sectional area).1,2 Intervention studies of lipid-lowering agents have reported variable outcomes but have generally demonstrated reductions in progression or actual regression of carotid IMT associated with fixed-dose statin therapy3–5 or additional fixed-dose niacin therapy,6,7 usually compared with placebo. The impact of blood pressure-lowering therapy on carotid IMT and mass is somewhat less conclusive, because most trials have compared one agent to another with either no difference between treatment arms11,12 or slightly more favorable results with dihydropyridines or angiotensin-converting enzyme inhibitors compared with diuretic or β-blocker therapy.13–15 In contrast, blood pressure lowering compared with placebo has been uniformly beneficial.4,16,17 Furthermore, IMT reduction for a given change in overall carotid mass may be exaggerated by use of vasodilator medications or understated with use of nonvasodilator antihypertensive agents.

Although hypertension is a major stimulus to left ventricular (LV) hypertrophy,18 dyslipidemia may indirectly stimulate LV hypertrophy if atherosclerosis causes recurrent ischemia.19,20 Blood pressure lowering has been repeatedly documented to reduce LV mass,21 and regression of LV hypertrophy improved clinical outcome, independent of in-treatment blood pressure.22 The impact of lipid lowering on LV mass has not been systematically examined.

The Stop Atherosclerosis in Native Diabetics Trial was a randomized trial of standard versus aggressive low-density lipoprotein (LDL) cholesterol and blood pressure targets in American Indians with type 2 diabetes mellitus.23 The combination of aggressive lowering of LDL cholesterol (≈70 mg/dL versus ≈100 mg/dL) and systolic blood pressure (≈115 mm Hg versus ≈130 mm Hg) over 3 years was
associated with regression in carotid IMT, the primary end point, and arterial mass, whereas both increased in the standard care group (P<0.001). LV mass, a secondary end point, regressed to a greater extent in the aggressive care group (P<0.03).24

Thus, the Stop Atherosclerosis in Native Diabetics Trial provides an opportunity to systematically examine the relative impacts of blood pressure lowering and lipid lowering on changes in arterial and LV mass by combining the 2 treatment arms and examining the magnitude of reductions in end points in a continuous rather than categorical manner. In addition, achieved levels and magnitudes of changes in systolic blood pressure and LDL cholesterol can be examined in relation to decreases in arterial and LV mass. For the present study, we chose to examine arterial mass rather than IMT, insofar as arterial mass provides a more comprehensive measure of the impacts of aging and distending pressure on arterial hypertrophy, particularly in the setting of antihypertensive therapy.25 Based on existing data, we hypothesized that lipid lowering would have a greater impact on regression of arterial hypertrophy, whereas blood pressure lowering would have a greater impact on regression of ventricular hypertrophy.

**Methods**

**Study Population**

The study population has been described previously in detail.23 In brief, American Indians with type 2 diabetes mellitus and no preexisting clinical cardiovascular disease, LDL cholesterol >100 mg/dL and systolic blood pressure >130 mm Hg were enrolled at 4 clinical centers. Participants were randomly assigned to aggressive LDL cholesterol (<70 mg/dL) and systolic blood pressure (≤115 mm Hg) lowering versus standard care (LDL cholesterol ≤100 mg/dL and systolic blood pressure ≤130 mm Hg) and followed for 36 months. Blood pressures were obtained in the seated position from the right brachial artery after 5 minutes of rest by trained personnel using an Omron 907 device (OMRON Healthcare, Inc, Kyoto, Japan). The mean of the second and third of 3 consecutive readings was recorded. Fasting blood samples were obtained to measure LDL cholesterol.

Interventions to lower and maintain LDL cholesterol and systolic blood pressure targets were based on National Cholesterol Education Program Adult Treatment Panel III26 and Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure27 algorithms, respectively. Only those participants with baseline and 36-month determinations of carotid mass and LV mass were included in the present analyses. End-study LDL cholesterol values are the average of the 24-, 30-, and 36-month determinations; end study systolic blood pressure values are the average of readings over the last 6 months of the study.24 In view of the importance of lowering non–high-density lipoprotein (HDL) cholesterol, particularly in diabetic individuals,28 the relation of non-HDL cholesterol targets to changes in arterial and LV mass was also examined. All of the participants provided informed written consent. The study was approved by all of the participating institutional review boards, the National Institutes of Health, and all of the participating American Indian communities.

**Ultrasound Studies**

Carotid and cardiac ultrasound studies were performed at baseline and 36-month visits according to standard protocols by centrally trained sonographers. All of the studies were reviewed by 2 highly experienced physician readers (M.J.R. and R.B.D.), blinded to treatment arm, at the central reading center. In brief, end-diastolic B-mode images of the distal right and left common carotid arteries were acquired in real time and digitized. A standardized 1-cm segment, selected to avoid areas with discrete atherosclerotic plaque, was measured using an automated edge detection system (100 separate dimensional measurements) with manual override capability. Arterial mass was calculated from end-diastolic wall thickness and lumen diameter, as described previously.29 Values of the 2 arteries were averaged to obtain mean carotid artery mass.

As described previously,24 the parasternal acoustic window was used to record ≥10 consecutive beats of 2D and M-mode recordings of LV internal diameter and wall thicknesses at or just below the tips of the mitral leaflets in both long- and short-axis views. LV internal dimension and septal and posterior wall thicknesses were measured at end diastole according to American Society of Echocardiography recommendations.31 LV mass was calculated using the following formula:

\[
LV\text{ mass} = 0.8 \times \left\{1.04 \times (LVID_d + PWT_d + SWT_d)^3 - (LVID_d)^3\right\} + 0.6 \text{ g.}
\]

where \(LVID\) is LV internal dimension, \(PWT\) is posterior wall thickness, \(SWT\) is septal wall thickness, and subscript \(d\) represents end diastole.

**Statistical Analyses**

Changes in carotid artery mass, LV mass, systolic blood pressure, and LDL cholesterol were calculated as the difference between 36-month and baseline values. Data are presented as mean±SD or percentages. Bivariate relations between changes in variables were determined by computing Pearson correlation coefficient. Multivariate relations were assessed by linear regression with indicator variables for strata of achieved LDL cholesterol and systolic blood pressure; in alternative models, strata of achieved non-HDL cholesterol were substituted for the strata of achieved LDL cholesterol. Two-tailed \(P<0.05\) was considered significant. Statistical analyses were performed with SPSS, version 12.0 (SPSS Inc, Chicago, IL).

**Results**

**Study Population and Changes in Carotid IMT and LV Mass**

The present analysis includes 413 Stop Atherosclerosis in Native Diabetics Trial participants with baseline and 36-month imaging data. Mean age at baseline was 56±9 years; 146 participants were men and 267 were women. Mean body mass index was 33.3±6.4 kg/m², 20.8% were current smokers, and 85.2% were taking oral hypoglycemic agents or insulin. At baseline there were significant correlations between systolic blood pressure and both LV and arterial mass (\(r=0.13, P=0.002\) and \(r=0.30, P<0.001\), respectively) and between LV and arterial mass (\(r=0.24, P<0.001\)), without significant associations of LDL cholesterol with the other variables. The participants were equally divided between the aggressive (n=207) and standard (n=206) arms of the trial. As described in Table 1, LDL cholesterol, non-HDL cholesterol, systolic blood pressure, and LV mass significantly decreased, whereas arterial mass significantly increased over the course of the trial (all \(P<0.001\)).

**Determinants of Changes in Carotid IMT and LV Mass**

By virtue of the trial design, changes in LDL cholesterol and systolic blood pressure were related (\(r=0.144; P=0.004\)). In bivariate analyses, a decrease in systolic blood pressure was significantly related to decreases in both LV mass (\(r=0.125, P=0.016\)) and arterial mass (\(r=0.188, P<0.001\)); a decrease...
in LDL cholesterol was related to a decrease in arterial (r=0.133; P=0.008) but not LV mass (r=0.097; P=0.066), and a decrease in non-HDL cholesterol was related to decreases in both arterial mass (r=0.099; P=0.048) and LV mass (r=0.117; P=0.027).

Because of the importance of baseline values of arterial and LV mass in determining the extent of change in these parameters and the association of age and body size with absolute values of these parameters, multivariate analyses were performed to explore these relationships. The magnitude of decrease in arterial mass (final minus baseline values) was significantly related to higher baseline arterial mass, higher baseline systolic blood pressure, and achieved levels of both systolic blood pressure and LDL cholesterol (Table 2). The magnitude of decrease in LV mass (final minus baseline values) was significantly related to higher baseline LV mass, measures of body size, and achieved levels of systolic blood pressure but not LDL cholesterol. Although decreases in arterial and LV mass were significant only in the lowest achieved systolic blood pressure group (<115 mm Hg), there was a clear trend for lower arterial and LV mass in relation to decreasing values of achieved systolic pressure. In additional analyses (Tables 2 and 3), wherein non-HDL cholesterol targets were substituted for LDL cholesterol targets, findings were similar.

To better approximate normality of distribution and to reduce collinearity, we repeated analyses using normalized values of changes in arterial mass, LV mass, systolic blood pressure, and LDL cholesterol, calculated as (final − baseline values)/baseline value, expressed as a percentage. The normal-

---

**Table 1. Baseline and 36-Month Values and Their Changes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>36-mo</th>
<th>Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>103±28</td>
<td>87±26</td>
<td>−16±37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dL</td>
<td>137±31</td>
<td>119±33</td>
<td>−18±41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP†</td>
<td>130±15</td>
<td>122±12</td>
<td>−7±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial mass, mm²</td>
<td>17.25±4.60</td>
<td>17.72±5.01</td>
<td>0.47±2.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial mass index, mm²/m²</td>
<td>8.86±2.41</td>
<td>9.10±2.67</td>
<td>0.24±1.51</td>
<td>0.001</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>157±38</td>
<td>151±38</td>
<td>−6±23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>80±17</td>
<td>77±15</td>
<td>−2±6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure; LV, left ventricular.

---

**Table 2. Multivariate Determinants of Changes in Arterial Mass**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Coefficient</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline arterial mass, mm²</td>
<td>−0.064</td>
<td>0.033</td>
<td>0.011</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.032</td>
<td>0.016</td>
<td>0.055</td>
</tr>
<tr>
<td>Baseline systolic BP, mm Hg†</td>
<td>−0.023</td>
<td>0.009</td>
<td>0.016</td>
</tr>
<tr>
<td>125 to 129 mm Hg (n=71)</td>
<td>−0.343</td>
<td>0.408</td>
<td>0.401</td>
</tr>
<tr>
<td>120 to 124 mm Hg (n=56)</td>
<td>−0.394</td>
<td>0.447</td>
<td>0.027</td>
</tr>
<tr>
<td>115 to 119 mm Hg (n=56)</td>
<td>−0.777</td>
<td>0.454</td>
<td>0.088</td>
</tr>
<tr>
<td>&lt;115 mm Hg (n=123)</td>
<td>−1.400</td>
<td>0.420</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex*</td>
<td>0.037</td>
<td>0.399</td>
<td>0.926</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.013</td>
<td>0.021</td>
<td>0.546</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.524</td>
<td>2.097</td>
<td>0.468</td>
</tr>
<tr>
<td>Baseline LDL cholesterol, mg/dL</td>
<td>0.001</td>
<td>0.005</td>
<td>0.912</td>
</tr>
<tr>
<td>Achieved LDL cholesterol‡</td>
<td>−0.385</td>
<td>0.320</td>
<td>0.229</td>
</tr>
<tr>
<td>&lt;70 mg/dL (n=133)</td>
<td>−0.829</td>
<td>0.362</td>
<td>0.023</td>
</tr>
<tr>
<td>Achieved non-HDL cholesterol§</td>
<td>−0.340</td>
<td>0.324</td>
<td>0.295</td>
</tr>
<tr>
<td>&lt;100 mg/dL (n=132)</td>
<td>−0.823</td>
<td>0.364</td>
<td>0.025</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure.

---

**Table 3. Multivariate Determinants of Changes in Left Ventricular Mass**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Coefficient</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LV mass, g</td>
<td>−0.355</td>
<td>0.035</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.130</td>
<td>0.125</td>
<td>0.297</td>
</tr>
<tr>
<td>Baseline systolic BP, mm Hg†</td>
<td>−0.057</td>
<td>0.074</td>
<td>0.441</td>
</tr>
<tr>
<td>125 to 129 mm Hg (n=69)</td>
<td>−1.793</td>
<td>3.239</td>
<td>0.580</td>
</tr>
<tr>
<td>120 to 124 mm Hg (n=50)</td>
<td>−5.751</td>
<td>3.665</td>
<td>0.117</td>
</tr>
<tr>
<td>115 to 119 mm Hg (n=56)</td>
<td>−6.469</td>
<td>3.547</td>
<td>0.089</td>
</tr>
<tr>
<td>&lt;115 mm Hg (n=119)</td>
<td>−8.837</td>
<td>3.433</td>
<td>0.010</td>
</tr>
<tr>
<td>Sex*</td>
<td>−8.386</td>
<td>3.187</td>
<td>0.009</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>1.193</td>
<td>0.192</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, m</td>
<td>40.120</td>
<td>17.731</td>
<td>0.024</td>
</tr>
<tr>
<td>Baseline LDL cholesterol, mg/dL</td>
<td>0.037</td>
<td>0.037</td>
<td>0.318</td>
</tr>
<tr>
<td>Achieved LDL cholesterol‡</td>
<td>−0.385</td>
<td>0.320</td>
<td>0.229</td>
</tr>
<tr>
<td>&lt;70 mg/dL (n=133)</td>
<td>−0.829</td>
<td>0.362</td>
<td>0.023</td>
</tr>
<tr>
<td>Achieved non-HDL cholesterol§</td>
<td>−0.340</td>
<td>0.324</td>
<td>0.295</td>
</tr>
<tr>
<td>&lt;100 mg/dL (n=132)</td>
<td>−0.823</td>
<td>0.364</td>
<td>0.025</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure.

*0= male; 1= female.
†Data are compared to achieved systolic BP of ≥130 mm Hg.
‡Data are compared to achieved LDL cholesterol of ≥100 mg/dL.
§Data are compared to achieved non-HDL cholesterol of ≥130 mg/dL (in separate model without LDL cholesterol).
ized change in systolic blood pressure was the only significant correlate of the normalized change in arterial mass ($P<0.001$), whereas both the normalized change in systolic blood pressure ($P=0.03$) and baseline body mass index ($P=0.02$) remained related to the normalized change in LV mass.

**Discussion**
The present study confirms the ability of pharmacological blood pressure lowering to reduce LV mass, as well as the importance of baseline LV mass in determining the extent of regression, and extends these observations to an exclusively diabetic population. Furthermore, our results suggest a graded association between the extent of systolic blood pressure lowering and extent of regression of arterial and LV mass, with no clear blood pressure threshold below which regression will not occur. Our study also provides systematic data on the lack of association between changes in LDL cholesterol and changes in LV mass.

The association of systolic blood pressure lowering with arterial mass change was slightly greater than that with LDL cholesterol lowering ($\beta=0.17$, $P=0.002$ for downward trend in systolic pressure and $\beta=0.12$, $P=0.018$ for downward trend in LDL cholesterol). It has been suggested that elevations in LDL cholesterol are primarily related to vascular thickening in the setting of significant blood pressure elevation ("response to injury hypothesis"). Because moderate-severe hypertension was not a feature of the Stop Atherosclerosis in Native Diabetics population even before randomized study treatment, the overall relation of LDL cholesterol to vascular mass may have been blunted. In fact, there was no relation of LDL cholesterol to mean arterial mass at baseline in the current study ($r=0.028$; $P=0.577$).

Understanding the relationships among systolic blood pressure, LDL cholesterol, and arterial mass requires consideration of the distinction between atherosclerosis and arteriosclerosis. Age-related changes in the structure and content of vessel wall and lumen diameter, components of arterial mass, differ from those attributed to atherosclerosis. Such age-related changes result in arterial stiffening, which increases pulse wave velocity, thereby resulting in earlier return of wave reflections and providing a pathophysiologic explanation for the well-documented age-related increase in systolic and decrease in diastolic blood pressures. In fact, age and systolic blood pressure appear to be the major determinants of both arterial stiffening and hypertrophy, whereas lipid components have a limited role. Thus, it follows that systolic blood pressure lowering would have a greater impact than LDL cholesterol lowering on arterial structure, particularly on common carotid artery thickening, which is more likely attributed to arteriosclerosis than atherosclerosis.

Very few other studies have examined the impact of combined blood pressure and lipid lowering on arterial structure. Fixed doses of long-acting metoprolol (25 mg daily) and fluvastatin (40 mg daily) were compared with placebo in the $\beta$-Blocker Cholesterol-Lowering Asymptomatic Plaque Study. Progression of the common carotid artery IMT was reduced in the fluvastatin group but not the $\beta$-blocker group; however, systolic blood pressure was not significantly lowered by metoprolol compared with placebo after 36 months of therapy. In contrast, metoprolol, but not fluvastatin, reduced carotid bifurcation IMT after 36 months of therapy. Of note, the authors reported no additive effect of therapy with both agents on carotid IMT. In the Plaque Hypertension Lipid Lowering Italian Study, the addition of pravastatin to fosinopril did not result in lesser progression of carotid IMT than with fosinopril alone. Other studies examining the effect of lipid lowering on carotid IMT have either not reported associated changes in blood pressure in treatment arms to allow examination of the potential importance of blood pressure changes in accounting for study findings or reported no difference in blood pressure change in treatment arms.

Potential limitations of the present study may limit its generalizability. Levels of LDL cholesterol at baseline were relatively low in comparison with some but not all previous studies. Thus, it is possible that previous statin therapy and/or relatively low baseline LDL cholesterol levels may have limited the ability to detect stronger relationships between LDL change and regression of arterial and LV mass. In this context, however, it is noteworthy that relatively low baseline systolic blood pressure levels did not interfere with the ability of targeted blood pressure lowering to reduce both arterial and LV mass.

**Perspectives**
Achieved levels of systolic BP are important determinants of the extent of regression of arterial and ventricular mass during prolonged antihypertensive therapy in diabetic individuals. Achieved levels of LDL cholesterol influence regression of arterial but not ventricular mass. Our findings suggest that there is no threshold of systolic BP below which regression of cardiovascular target organ damage cannot be achieved.

**Sources of Funding**
Funding was provided by the National Heart, Lung, and Blood Institute, National Institutes of Health, grant 1U01 HL67031-01A1. Medications were donated by First Horizon Pharmacy (Triglide); Merck and Co (Cozaar/Hyzaar); and Pfizer, Inc (Lipitor).

**Disclosures**

**References**
5. Salonen R, Nyysönen K, Pirkkala E, Rummukainen J, Belder R, Park J-S, Salonen JT. Kuopio Atherosclerosis Prevention Study (KAPS): a...


24. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard M, Roman MJ, Seward J, Shenewise JS, Solomon SD, Spencer KT, St John Sutton M, Stewart WJ. Recommendations for chamber quantification: a report form the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Working Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2006;19:1440–1463.


Differential Impacts of Blood Pressure and Lipid Lowering on Regression of Ventricular and Arterial Mass: The Stop Atherosclerosis in Native Diabetics Trial
Mary J. Roman, Barbara V. Howard, Wm. James Howard, Mihriye Mete, Jerome L. Fleg, Elisa T. Lee and Richard B. Devereux

Hypertension. published online July 25, 2011;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2011/07/21/HYPERTENSIONAHA.111.172486

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/